Tidsskriftet
DEN NORSKE LEGEFORENING

Harmonised reference ranges for antiepileptic drugs

DEBATT

ARNE REIMERS

E-mail: arne.reimers@stolav.no
Arne Reimers (born 1965), Dr. Philos., is a specialist in clinical pharmacology and senior consultant at the Department of Clinical Pharmacology, St. Olavs University Hospital, and associate professor at the Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology.
The author has completed the ICMJE form and reports no conflicts of interest.

JON ANDSNES BERG

Jon Andsnes Berg (born 1978) is a specialist in clinical pharmacology and senior consultant in the Laboratory of Clinical Biochemistry, Section of Clinical Pharmacology, Haukeland University Hospital.
The author has completed the ICMJE form and reports no conflicts of interest.

MARGRETE LARSEN BURNS

Margrete Larsen Burns (born 1980) is a specialist in clinical pharmacology and senior consultant/head of the Section of Clinical Pharmacology, National Centre for Epilepsy, Department of Pharmacology, Oslo University Hospital.
The author has completed the ICMJE form and reports no conflicts of interest.

CECILIE JOHANNESSEN LANDMARK

Cecilie Johannessen Landmark (born 1971), cand.pharm., PhD, medical advisor at the National Centre for Epilepsy and Department of Pharmacology, Oslo University Hospital, and associate professor at the programme for Pharmacy, Faculty of Health Sciences, Oslo and Akershus University College
The author has completed the ICMJE form and reports no conflicts of interest.

Antiepileptic drugs are the cornerstone of epilepsy treatment and are also used in a range of other indications. Measurement of the serum concentrations of antiepileptic drugs has a long tradition as a tool in the treatment of epilepsy in Norway. New and updated national reference ranges for serum concentration measurements of antiepileptic drugs in the treatment of epilepsy are now available.

In 2016, according to the Norwegian Prescription Database, there were 127 138 users of antiepileptic drugs in Norway, equivalent to 24 users per 1 000 inhabitants (1). The use of these drugs increases every year, with the most extensive increase related to the treatment of neuropathic pain and psychiatric disorders (2, 3). The use of these drugs to treat epilepsy is stable at approximately 7 DDD/1 000 inhabitants/day (2).

Owing to unfavourable pharmacokinetic properties, marked interaction potential and narrow therapeutic windows, measurement of the serum concentration of antiepileptic

drugs is a useful tool in the management of epilepsy (4, 5). The reference ranges for first-generation antiepileptic drugs (those introduced up to and including in 1984) are well established and fairly consistent worldwide, with only few and minor differences between laboratories (5).

Since 1984, 15 new antiepileptic drugs have entered the market. The reference ranges for some of these drugs may be considered to be equally well established as those of the first-generation drugs. For the newer drugs, however, there is little published evidence. Only in a few cases are there clinical data available that may form a basis for defining reference ranges. As a consequence, greater variation is observed both between laboratories and in scientific articles. For some of the latest antiepileptic drugs, even preliminary suggestions for reference ranges are not yet available.

Updated harmonised reference ranges in Norway

In February 2015, the Norwegian Association of Clinical Pharmacology launched the Pharmacology Portal as a nationwide web portal for pharmacological and toxicological analyses (6, 7). It is thus naturally desirable for the laboratories represented in the portal to use the same reference ranges. This allows for better collaboration between laboratories and ensures that those who request the analyses receive unambiguous results. Harmonised national reference ranges have so far been established for benzodiazepines, z-hypnotics, opioids and anticoagulants (8–10).

The working group on antiepileptic drugs has recently submitted its report to the Board of the Norwegian Association of Clinical Pharmacology. The report is based on existing reference ranges in Norway and on an international consensus report on the use of therapeutic drug monitoring (5), as well as updated information from the literature and from epilepsy centres in other countries. The working group has used this information to perform an overall evaluation of existing reference ranges, prioritised according to the level of clinical evidence. A detailed description of the methods can be found in the report (11), which has been approved by the Board of the Norwegian Association of Clinical Pharmacology. The new reference ranges can therefore be considered valid, and entries for relevant drugs have been updated in the Pharmacology Portal.

In common with other medicines, antiepileptic drugs are used not only as monotherapy, but also in combination with one another or with other medicines. However, when establishing reference ranges, potential pharmaco*dynamic* interactions in polytherapy are disregarded. As in all pharmacotherapy, therefore, clinical assessment of the patient should guide the treatment.

An overview of the former reference ranges and the new, updated national reference ranges is shown in Table 1 (11). The reference ranges apply to samples obtained just prior to the next regular dose and 12–24 hours after the previous dose. The recommendation is for most of the existing reference ranges to be retained, or adjusted only slightly. Total concentration is measured as standard, but free concentrations of drugs with a high degree of protein binding can also be measured for particular indications.

Table 1

Former reference ranges for antiepileptic drugs in Norway and the new, harmonised reference ranges (11)1. Changes are marked in italic bold text.

Antiepileptic drug	Brand name (example)	Introduced	Former reference range (µmol/l)	New reference range (µmol/l)
Brivaracetam[2]	Briviact	2016	—	—
Eslicarbazepine	Zebinix	2010	30-100; 50-140; 10-100; 45-140	***12–100***

Antiepileptic drug	Brand name (example)	Introduced	Former reference range (μmol/l)	New reference range (μmol/l)
Ethosuximide	Suxinutin	1955	300-600	***280-700***
Felbamate	Taloxa	1993	125-250	125-250
Phenobarbital	Fenemal	1912	50-130	50-130
Phenytoin Free phenytoin	Fenantoin	1938	40-80 ca. 10%	40-80 ca.10%
Gabapentin	Neurontin	1994	20-120	20-120
Carbamazepine Free carbamazepine	Tegretol	1962	15-45 24-33% (= 4-12.5 μmol/l)	15-45 24-33% (= 4-12.5 μmol/l)
Clobazam N-desmethylclobazam	Frisium	1984	0.1-1 1-10	0.1-1 1-10
Clonazepam	Rivotril	1973	60-220 nanomol/l	***40-120*** nanomol/l
Lacosamide	Vimpat	2009	10-40	10-40
Lamotrigine	Lamictal	1992	10-50; 10-60	10-***50***
Levetiracetam	Keppra	2000	30-240	30-240
Oxcarbazepine[3]	Trileptal	1989	45-140; 50-140	***12***-140
Perampanel[2]	Fycompa	2012	—	***0.25-2.85***
Pregabalin	Lyrica	2004	10-30	***10-35***
Rufinamide[2]	Inovelon	2007	20-130	***12-130***
Stiripentol[2]	Diacomit	2008	—	***15-95***
Sulthiame[2]	Ospolot	1960	—	***5-35***
Topiramate	Topimax	1995	15-60	***6-30***
Valproate Free valproate	Orfiril	1967	250/300-600/700 ca. 10%	***300-700*** ca. 10%
Vigabatrin[4]	Sabrilex	1991	—	—
Zonisamide	Zonegran	1990	45-180	45-180

1 When establishing reference ranges, potential pharmaco*dynamic* interactions in polytherapy are disregarded. As in all pharmacotherapy, therefore, clinical assessment of the patient must guide the treatment.

2 Analysis is under development and will shortly be available at the National Centre for Epilepsy, Oslo University Hospital

3 Reference range refers to the active metabolite licarbazepine (previously known as monohydroxy derivative, MHD)

4 Vigabatrin is an irreversible enzyme inhibitor, and no direct association has been established between its serum concentration and clinical efficacy

We hope that harmonisation of the reference ranges for antiepileptic drugs will contribute to better treatment for patients. Thorough documentation and research on new antiepileptic drugs in clinical practice will provide sorely needed knowledge on pharmacokinetic variability and its impact on clinical efficacy and tolerance, and lead to even better collaboration between laboratories (12, 13).

REFERENCES:

1. Reseptregisteret. www.reseptregisteret.no (30.3.2017).

2. Baftiu A, Johannessen Landmark C, Rusten IR et al. Changes in utilisation of antiepileptic drugs in epilepsy and non-epilepsy disorders-a pharmacoepidemiological study and clinical implications. Eur J Clin Pharmacol 2016; 72: 1245 - 54. [PubMed][CrossRef]

3. Landmark CJ, Fossmark H, Larsson PG et al. Prescription patterns of antiepileptic drugs in patients with epilepsy in a nation-wide population. Epilepsy Res 2011; 95: 51 - 9. [PubMed][CrossRef]

4. Landmark CJ, Johannessen SI, Tomson T. Dosing strategies for antiepileptic drugs: from a standard dose for all to individualised treatment by implementation of therapeutic drug monitoring. Epileptic Disord 2016; 18: 367 - 83 [PubMed].. [PubMed]

5. Patsalos PN, Berry DJ, Bourgeois BF et al. Antiepileptic drugs–best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia 2008; 49: 1239 - 76. [PubMed][CrossRef]

6. Farmakologiportalen. Norsk portal for legemiddel- og rusmiddelanalyser. www.farmakologiportalen.no (18.5.2017).

7. Karlsen Bjånes T, Mjåset Hjertø E, Lønne L et al. Pharmacology Portal: An Open Database for Clinical Pharmacologic Laboratory Services. Clin Ther 2016; 38: 222 - 6. [PubMed][CrossRef]

8. Farmakologiportalen. Nasjonale referanseområder - prosjektrapporter: http://www.farmakologiportalen.no/ nasjonale_referanseomrader/ (30.3.2017).

9. Helland A, Berg JA, Gustavsen I et al. Serumkonsentrasjonsmålinger av vanedannende legemidler. Tidsskr Nor Legeforen 2016; 136: 400 - 2. [PubMed][CrossRef]

10. Lundgaard H, Dyrkorn R, Stokes CL et al. Tryggere behandling med serumkonsentrasjonsmåling av de nye antikoagulasjonsmidlene? Tidsskr Nor Legeforen 2016; 136: 1556 - 60. [PubMed][CrossRef]

11. Farmakolgiportalen. Felles nasjonale referanseområder for antiepileptika. http://www.farmakologiportalen.no/ attachment.ap?id=13. (3.5.2017).

12. Svendsen T, Brodtkorb E, Baftiu A et al. Therapeutic Drug Monitoring of Lacosamide in Norway: Focus on Pharmacokinetic Variability, Efficacy and Tolerability. Neurochem Res 2017; E-publisert 27.3.. [PubMed]

13. Svendsen T, Brodtkorb E, Reimers A et al. Pharmacokinetic variability, efficacy and tolerability of eslicarbazepine acetate-A national approach to the evaluation of therapeutic drug monitoring data and clinical outcome. Epilepsy Res 2017; 129: 125 - 31. [PubMed][CrossRef]

Published: 28 June 2017. Tidsskr Nor Legeforen. DOI: 10.4045/tidsskr.17.0392
Received 27.4.2017, first revision submitted 15.5.2017, accepted 18.5.2017.